REMARKS

Applicants have added new claim 44. Applicants have previously canceled claim 2 and withdrawn claims 3, 5, 9, 12-18, 21-22 and 25-43. Following entry of this amendment, claims 1 and 3-44 will be pending in this application.

New claim 44 depends from claim 1 and recites that the combination of a cytokine-expressing cellular vaccine consists essentially of proliferation-incompetent tumor cells that express human GM-CSF and an anti-OX-40 antibody. Support for this amendment may be found throughout the specification, *e.g.*, at page 54, line 15 through page 55, line 8.

This claim addition does not add new matter.

This amendment (i.e., new claim 44) is made in accordance with 37 C.F.R. § 1.116. It narrows claims. It complies with requirements of form. It also presents a claim in condition for allowance or at least in better form for appeal. Applicants request its entry into this application and the allowance of claim 44 and the other pending claims.

THE REJECTIONS

35 U.S.C. §§ 103(a)

Claims 1, 4, 6-8, 10-11, 19-20, and 23-24

Claims 1, 4, 6-8, 10-11, 19-20, and 23-24 are rejected under 35 U.S.C. § 103(a) over Gri *et al.*, "OX40 ligand-transduced tumor cell vaccine synergizes with GM-CSF and requires CD40-Apc signaling to boost the host T cell antitumor response," J. Immunol., 170: 99-106 (2003) ("Gri") in view of US Patent Publication 2003/0035790 ("Chen"). Specifically, the Examiner argues that Gri does not

teach away, as applicants have argued, from combining anti-OX40 antibodies with GM-CSF expressing tumor cells, a combination that the Examiner finds in Gri in view of Chen. In particular, the Examiner dismissed applicants' arguments that the effect of anti-OX40 antibodies would be different from the effect of OX40 ligand because allegedly applicants have admitted that anti-OX40 antibody is interchangeable with anti-OX40 ligand. See claim 1's Markush group.

In arguing against applicants' demonstration that Gri teaches away from the Examiner's attempt to combine it with Chen, the Examiner has used the wrong focal point. The Examiner has improperly looked to applicant's invention, *e.g.*, claim 1, not the cited documents themselves. This has allowed impermissible hindsight to be the only foundation of the rejection. This is not proper when analyzing obviousness. Indeed, M.P.E.P. §2145 (X)(A) makes clear that "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper" (emphasis added). Here, the rejection has turned that admonition on its head. For that reason alone, applicants' request that the Examiner reconsider the rejection and allow the pending claim.

In such reconsideration, the Examiner should look to the cited documents themselves, not applicants' invention and claims. Those documents provide no basis or support for the Examiner's assertion that it would have been obvious to a person of ordinary skill in the art at the time of the invention to apply the teachings of Chen regarding administration of anti-OX40 antibodies to enhance the immune response against GM-CSF-expressing tumor cells to those of Gri and to thereby arrive at the instantly claimed method.

As applicants discussed previously, Gri teaches away from combining anti-OX40 antibodies with GM-CSF-expressing tumor cells. The last paragraph of Gri on page 105 to which the Examiner points in arguing that Gri teaches that OX40 ligand is functionally equivalent to anti-OX40 antibodies says no such thing. In fact, the last paragraph of Gri states, in part, that "[r]ecent adoptive immunotherapy experiments have shown that the coadministration of anti-OX40 Ab reduces the number of transferred T cells required to obtain remission of pulmonary metastasis and intracranial tumors" (citing Kjaergaard *et al.*, "Therapeutic Efficacy of OX-40 Receptor Antibody Depends on Tumor Immunogenicity and Anatomic Site of Tumor Growth," Cancer Research, 60:5514-5521 (2000) ("Kjaergaard"), previously submitted as **Exhibit A**). As applicant has demonstrated previously, Kjaergaard refers to experiments showing that anti-OX40 antibodies do not necessarily and inevitably treat cancers and that the therapeutic efficacy of anti-OX40 antibodies (referred to as OX40 receptor mAb in Kjaergaard) was influenced by a number of factors including the tumor burden, the intrinsic immunogenicity of the tumor as well as the histological site of tumor growth. In particular, Kjaergaard reports that "[w]hereas subdermal and intracranial growth of weakly immunogenic MCA 203 and MCA 205 sarcomas and GL261 glioma were susceptible to the mAb treatment, established ***pulmonary MCA 205 metastases were refractory to the same regimen of treatment***. Furthermore, the mAb administration had ***no impact on the growth of the poorly immunogenic B16/D5 melanoma***." (emphasis added; Abstract, p. 5514). Kjaergaard then concludes that the "successful treatment is mAb dose-dependent and effected by the intrinsic immunogenicity of tumors. It is also evident that the response of a particular tumor to the treatment varies and is dependent on the histological location of tumor growth." (see, p. 5517, first full paragraph). Thus, based on Kjaergaard, the very document referred to in the last paragraph of Gri, anti-OX40 antibodies are not functionally equivalent to OX40 ligand. Rather, the equivalence of OX-40 ligand and anti-OX40 antibodies, that is presumed by the Examiner from Gri,

is contradicted by the results reported in Kjaergaard. That is, the effect of OX-40 ligand on the treatment of cancer would not have allowed one of skill in the art to predict the effect of anti-OX-40 antibodies on the presence of GM-CSF producing cells in the treatment of cancer.

Applicants' specification does not change what Gri (and Kjaergaard) report. The specification recites only that "[i]n order to optimize the clinical efficacy of a cytokine-expressing cellular vaccine/OX40L or anti-OX40 combination, a number of treatment regimens are evaluated in syngeneic tumor models (as further described in Example 7 and Gri, G. et al. J. Immunol. 2003, Jan 1 ;170(1):99-106)." This statement does not say or even imply that Gri recites that anti-OX40 antibody is interchangeable with OX40 ligand. It relates to the two syngenic tumor models of Example 7 and Gri, not the therapeutic agents used in those models. Indeed, both Gri and Example 7 of the specification provide tumor models for analyzing the clinical efficiency of agents against cancer. Gri, however, does not use OX40 antibodies as a therapeutic agent in any of its models. Hence, the use of those models says nothing about whether or not OX40 ligand and anti-OX40 antibodies are equivalent. In fact, were the mere use of a model to be a statement of functional equivalence, every compound tested in a model would be the equivalent of every other compound tested in the model. That is certainly not the case. Accordingly, as applicants have demonstrated previously, Gri and Kjaergaard teach away from using anti-OX-40 antibodies in combination with GM-CSF in the treatment of cancer. Applicants' claims are also no help to the Examiner. They recite applicants' invention not what the cited documents reported or suggested to the skilled worker. Chen does not remedy these deficiencies.

First and foremost, Chen teaches away from any combination with Gri. Chen always requires IL-12 in its treatment methods. For example, the Examiner points to paragraphs [0031] and [0277] of Chen, which recite:

> In a preferred embodiment, the present invention provides a method for preventing or treating cancer or an infectious disease in a subject, said method comprising administering to said subject an effective amount of a recombinant adenovirus engineered to express IL-12, an effective amount of a recombinant adenovirus engineered to express GM-CSF, and an effective amount of an agonistic anti-4-1BB monoclonal antibody or antigen-binding fragment thereof. In another preferred embodiment, the present invention provides a method for preventing or treating cancer or an infectious disease in a subject, said method comprising administering to said subject an effective amount of a recombinant adenovirus engineered to express IL-12, an effective amount of a recombinant adenovirus engineered to express GM-CSF, and an effective amount of an agonistic anti-OX40 monoclonal antibody or antigen-binding fragment thereof. In yet another preferred embodiment, the present invention provides a method for preventing or treating cancer or an infectious disease in a subject, said method comprising administering to said subject an effective amount of a recombinant adenovirus engineered to express IL-12, an effective amount of a recombinant adenovirus engineered to express GM-CSF, an effective amount of an agonistic anti-4-1BB monoclonal antibody or an antigen-binding fragment thereof, and an effective amount of an agonistic anti-OX40 monoclonal antibody or an antigen-binding fragment thereof. (emphasis added)

Thus, paragraphs [0031] and [0277] of Chen refer to three specific embodiments. All require IL-12. Nowhere does Chen suggest to the skilled worker that GM-CSF and a second agent, in the absence of IL-12, should, or could, be used.

Examples 10 and 11 of Chen also confirm its three-part IL-12-based method. In Example 10, Chen refers to injecting MCA26 tumor-bearing mice intratumorally with an adenovirus expressing mGM-CSF. Chen further recites inducing metastatic colon cancer by implanting MCA26 tumor cells into the left lobe of the liver

and then subsequently injecting adenovirus expressing mGM-CSF into tumor-bearing mice. IL-12 and anti-4-1BB antibodies were injected *8 days after* the GM-CSF injection (see, *e.g.*, Example 11 and Fig. 22). Therefore, Chen does not teach or suggest a method of treatment using GM-CSF and a second agent, as alleged by the Examiner., Rather, Chen always requires IL-12. Further, Chen refers only to treatments whereby the additional therapeutic agents are not even administered in the same composition, but 8 days after administration of the GM-CSF adenovirus. Thus, Chen does not teach or suggest the administration of a cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF in combination with an additional agent, as recited in the instant claims. Instead of administering proliferation-incompetent tumor cells to express GM-CSF and an additional therapeutic agent, Chen refers injecting adenovirus expressing mGM-CSF directly into tumor-bearing animals followed by treatment with IL-12 and an additional agent 8 days after the GM-CSF injection. As discussed above, Gri teaches away from using anti-OX-40 antibodies in combination with GM-CSF in the treatment of cancer. Accordingly, Chen fails to correct the deficiencies of Gri.

The Examiner also asserts that Chen teaches that GM-CSF may be expressed in mammalian cells and points to paragraphs [0212]-[0214] as supposed support. The Examiner is mistaken. The mention of mammalian cells appears only in paragraph [0213] of Chen and states, in part, that "[a] variety of host-vector systems may be utilized to express the protein-coding sequence. These include but are not limited to ***mammalian cell systems*** infected with virus (e.g., vaccinia virus, adenovirus, adeno-associated virus (AAV), retrovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA." (emphasis added). Thus, paragraph [0213] of Chen reports only that the protein-coding sequence of

GM-CSF may be expressed using viruses that infect mammalian cell systems. In fact, Chen refers to injecting an adenovirus-expressing mGM-CSF (*i.e.*, a virus) directly into tumor-bearing animals (*i.e.*, mammalian cell system) and does not support the Examiner's assertion that Chen teaches GM-CSF may be expressed in mammalian cells, let alone, proliferation-incompetent tumor cells. Further paragraph [0214] of Chen refers to expressing IL-12 in combination with a second agent (*i.e.*, 4-1BB ligand and/or OX40 ligand) or expressing IL-12, GM-CSF, and a third agent (*i.e.*, 4-1BB ligand and/or OX40 ligand) in vivo. Accordingly, the paragraphs relied on by the Examiner do not refer the claimed methods using a composition comprising a cellular vaccine in combination with anti-OX40-antibodies.

The Examiner's assertion that Chen discusses a cancer vaccine approach wherein cancer cells are isolated from patients, transduced in vitro, irradiated, and administered to patients is also irrelevant. The claimed invention relates to the administration of a cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that are selected from the group consisting of allogeneic and bystander cells. Chen does not teach or suggest this feature of the claimed invention. By contrast, the Chen cancer cells are autologous cells and are not allogeneic and bystander cells, as recited by the pending claims. Further, Chen teaches away from using transduced irradiated cells. Paragraph [0005], relied on by the Examiner, recites "[the "cancer vaccine" approach] is not only laborious but the treatment is also individualized as cancer cells need to be cultured and expanded from each patient for therapeutic purposes. A more attractive strategy is to deliver the cytokine genes in vivo." Thus, Chen explicitly teaches away from using cellular vaccines or compositions comprising cellular vaccines and anti-OX40 antibodies.

Finally, the Examiner asserts that nonobviousness cannot be shown by attacking the cited documents individually where the rejections are based on their

combination. Applicants have not attacked Gri and Chen individually. They have attacked the combination. As discussed above, Gri teaches away from using anti-OX40 antibodies because of their affect on T-cells, and Chen teaches away from using the cellular vaccines of Gri. Accordingly, because Gri teaches away from Chen and Chen teaches away from Gri, the Examiner's combination is improper. For at least the above reasons, neither Gri nor Chen, alone or in combination, renders the claimed invention obvious. In view of applicants' demonstration that Gri and Chen teach away from each other and applicants' claimed invention, the Examiner's assertions regarding what the skilled worker would know about the use of human GM-CSF based on use of a murine GM-CSF are moot. Accordingly, applicants request that the Examiner reconsider and withdraw this rejection.

35 USC §101 - Nonstatutory Double Patenting
Claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24

Claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-33 of copending U.S. Application No. 10/404,662.

Applicants request that this provisional rejection be held in abeyance until this application or copending application 10/404,662 is allowed. At that time, applicants will file a Terminal Disclaimer or otherwise respond to the rejection as is appropriate and proper.

CONCLUSION

In view of the foregoing remarks, applicants request that the Examiner favorably reconsider this application and allow the claims pending herein. If the

Examiner believes that a telephone conference would expedite allowance of this application, she is invited to telephone the undersigned at any time.

Respectfully submitted,

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